

Remington's Pharmaceutical Sciences

A treatise on the theory and practice of pharmaceutical sciences, with essential information about pharmaceutical and medicinal agents; also a guide to the professional responsibilities and services of the pharmacist as a member of the health team A text-book and reference work for pharmacists, physicians, and other medical scientists

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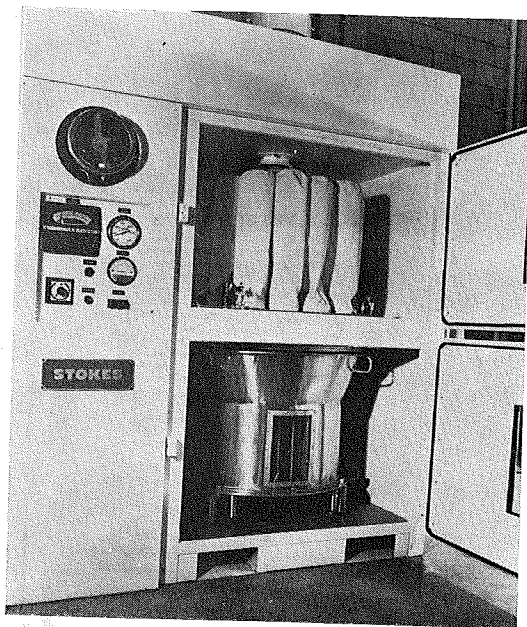


Fig. 89-12. Fluid bed dryer (courtesy, Stokes).

ingredients may be related to the moisture content of the products.

After drying, the granulation is reduced in particle size by passing it through a smaller mesh screen. Following dry screening the granule size tends to be more uniform. For dry granulations the screen size to be selected depends on the diameter of the punch. The following sizes are suggested.

Tablets up to $\frac{3}{16}$ -in. diam, use 20-mesh
 Tablets $\frac{3}{16}$ in. to $\frac{1}{4}$ in., use 16-mesh
 Tablets $\frac{1}{4}$ in. to $\frac{3}{8}$ in., use 14-mesh
 Tablets $\frac{3}{8}$ in. and larger, use 12-mesh

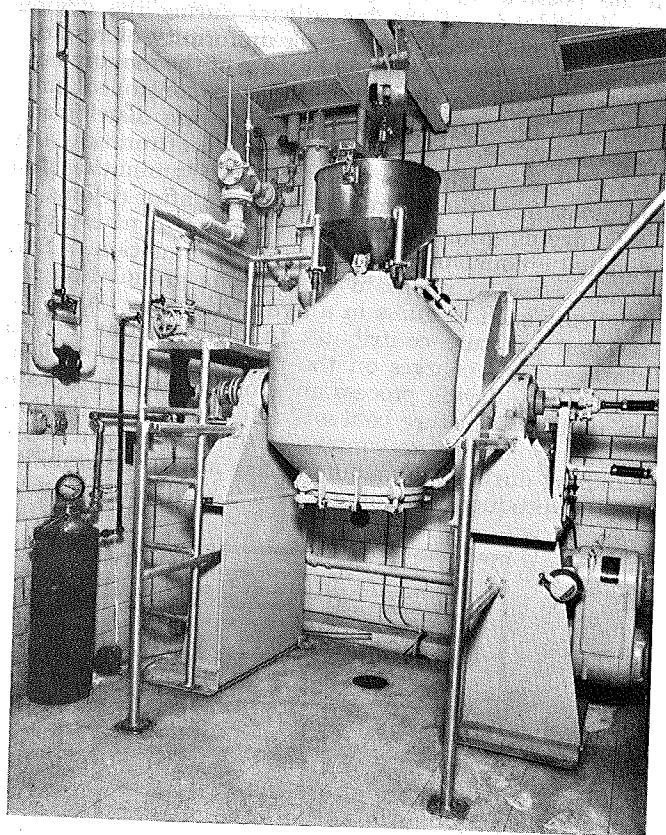


Fig. 89-13. Rovac dryer (courtesy, Ciba-Geigy).

For small amounts of granulation, hand screens may be used and the material passed through with the aid of a wooden block. With larger quantities, any of the comminuting mills with screens corresponding to those just mentioned may be used. Note that the smaller the tablet, the finer the dry granulation to enable more uniform filling of the die cavity; large granules give an irregular fill to a comparatively small die cavity. With compressed tablets of sodium bicarbonate, lactose, and magnesium trisilicate, a relationship has been demonstrated to exist between the particle size of the granulated material and the disintegration time and capping of the resultant tablets. For a sulfathiazole granulation, however, the particle-size distribution did not appear to influence hardness or disintegration.

After dry granulation, the lubricant is added as a fine powder. It is usually screened onto the granulation through 100-mesh nylon cloth to eliminate small lumps as well as to increase the covering power of the lubricant. As it is desirable for each granule to be covered with the lubricant, the lubricant is blended with the granulation very gently, preferably in a blender using tumbling action. Gentle action is desired to maintain the uniform granule size resulting from the dry-granulation step. It has been claimed that too much fine powder is not desirable because fine powder may not feed into the die evenly; consequently, variations in weight and density result. Fine powders, commonly designated as "fines," also blow out around the upper punch and down past the lower punch, making it necessary to clean the machine frequently. Air trapped in the tablets by the fine powder causes them to split apart after ejection from the machine. Fines, however, at a level of 10–20% are traditionally sought by the tablet formulator. The presence of some fines is necessary for the proper filling of the die cavity. Recently, even higher concentrations of fines were successfully used in tablet manufacture. Some investigators maintain that no general limits exist for the amount of fines that can be present in a granulation but must be determined for each specific formula.

Another approach toward the faster preparation of tablet granulations has come from the utilization of the air-suspension technique developed by Wurster.⁹ In this method particles of an inert material, or the active drug, are suspended in a vertical column with a rising air stream; while the particles are suspended, the common granulating materials in solution are sprayed into the column. There is a gradual particle buildup under a controlled set of conditions resulting in a tablet granulation which is ready for compression after addition of the lubricant. In addition to its use for the preparation of tablet granulations this technique also has been proposed for the coating of solid particles as a means of improving the flow properties of small particles (see page 1611). Methods for the preparation of compressed tablets have been reviewed in the literature.¹⁰

Dry-Granulation Method

When tablet ingredients are sensitive to moisture or are unable to withstand elevated temperatures during drying, and when the tablet ingredients have sufficient inherent binding or cohesive properties, slugging may be used to form granules. This method is referred to as dry granulation, precompression, or the double-compression method. It eliminates a number of steps but still includes (1) weighing, (2) mixing,

Tablet Formulations

Wet Granulation Method

CT Acetaminophen, 300 mg

Ingredients	In each	In 10,000
Acetaminophen	300 mg	3000 g
Polyvinylpyrrolidone	22.5 mg	225 g
Lactose	61.75 mg	617.5 g
Alcohol 3A—200 proof	4.5 ml	45 l
Stearic acid	9 mg	90 g
Talc	13.5 mg	135 g
Corn starch	43.25 mg	432.5 g

Blend acetaminophen, polyvinylpyrrolidone, and lactose together; pass through a 40-mesh screen. Add the alcohol slowly and knead well. Screen the wet mass through a 4-mesh screen. Dry granulation at 50°C overnight. Screen the dried granulation through a 20-mesh screen. Bolt the stearic acid, talc, and corn starch through 60-mesh screen prior to mixing by tumbling with the granulation. Compress using $\frac{1}{8}$ -in. standard concave punch. 10 tablets should weigh 4.5 g (courtesy, Abbott).

CT Ascorbic Acid USP, 50 mg

Ingredients	In each	In 7000
Ascorbic Acid USP (powder No. 80) ^a	55 mg	385 g
Lactose	21 mg	147 g
Starch (potato)	13 mg	91 g
Ethylcellulose N 100 (80–105 cps)	16 mg	112 g
Starch (potato)	7 mg	49 g
Talc	6.5 mg	45.5 g
Calcium stearate (impalpable powder)	1 mg	7 g
Weight of granulation		836.5 g

^a Includes 10% in excess of claim.

Granulate the above first three ingredients with ethylcellulose (5%) dissolved in anhydrous ethyl alcohol adding additional anhydrous alcohol to obtain good wet granules. Wet screen through 8 stainless steel screen and dry at room temperature in an air-conditioned area. Dry screen through 20 stainless steel screen and incorporate the remaining three ingredients. Mix thoroughly and compress. Use a flat beveled, $\frac{1}{4}$ -in. punch. 20 tablets should weigh 2.39 g.

Chewable Antacid Tablets

Ingredients	In each	In 10,000
Magnesium trisilicate	500 mg	5000 g
Aluminum hydroxide, dried gel	250 mg	2500 g
Mannitol	300 mg	3000 g
Sodium saccharin	2 mg	20 g
Starch paste, 5%	qs	qs
Oil of peppermint	1 mg	10 g
Magnesium stearate	10 mg	100 g
Corn starch	10 mg	100 g

Mix the magnesium trisilicate and aluminum hydroxide with the mannitol. Dissolve the sodium saccharin in a small quantity of purified water, then combine this with the starch paste. Granulate the powder blend with the starch paste. Dry at 140°F and screen through 16-mesh screen. Add the flavoring oil, magnesium stearate, and corn starch; mix well. Age the granulation for at least 24 hours and compress using $\frac{5}{8}$ -in. flat-face bevel-edge punch (courtesy, Atlas).

CT Hexavitamin NF

Ingredients	In each	In 7000
Ascorbic Acid USP (powder) ^a	82.5 mg	577.5 g
Thiamine Mononitrate USP (powder) ^a	2.4 mg	16.8 g
Riboflavin ^a	3.3 mg	23.1 g
Nicotinamide USP (powder) ^a	22 mg	154 g
Starch	...	97.4 g
Lactose	...	41.2 g
Zein	...	45 g
Vitamin A acetate:	6250 U	
Vitamin D ₂ ^a (use Pfizer crystals medium granules containing 500,000 U vitamin A acetate and 50,000 U vitamin D ₂ /g).	625 U	87.5 g
Magnesium stearate		7.5 g
Weight of granulation		1050 g

^a Includes following excess of claim: ascorbic acid 10%, thiamine hydrochloride 20%, riboflavin 10%, nicotinamide 10%, and vitamin A acetate-vitamin D₂ crystals 25%.

Thoroughly mix the first six ingredients and granulate with zein (10% in ethyl alcohol, adding additional alcohol if necessary to obtain good wet granules). Wet screen through 8 stainless steel screen and dry at 110–120°F. Dry screen through 20 stainless steel screen and add the vitamin crystals. Mix thoroughly, lubricate and compress. 10 tablets should weigh 1.50 g. Coat with syrup.

CT Theobromine-Phenobarbital

Ingredients	In each	In 7000
Theobromine	325 mg	2275 g
Phenobarbital	33 mg	231 g
Starch	39 mg	273 g
Talc	8 mg	56 g
Acacia (powder)	8 mg	56 g
Stearic acid	0.7 mg	4.9 g
Weight of granulation		2895.9 g

Prepare a paste with the acacia and an equal weight of starch. Use this paste for granulating the theobromine and phenobarbital. Dry and put through a 12-mesh screen, add the remainder of the material, mix thoroughly, and compress into tablets, using a $\frac{1}{2}$ -in. concave punch. 10 tablets should weigh 4.13 g.

Dry Granulation Method

CT Acetylsalicylic Acid

Ingredients	In each	In 7000
Acetylsalicylic Acid (crystals 20-mesh)	0.325 g	2275 g
Starch		226.8 g
Weight of granulation		2501.8 g

Dry the starch to a moisture content of 10%. Thoroughly mix this with the acetylsalicylic acid. Compress into slugs. Grind the slugs to 14–16-mesh size. Recompress into tablets, using a $\frac{1}{2}$ -in. punch. 10 tablets should weigh 3.575 g.

CT Sodium Phenobarbital

Ingredients	In each	In 7000
Phenobarbital sodium	65 mg	455 g
Milk sugar (granular, 12-mesh)	26 mg	182 g
Starch	20 mg	140 g
Talc	20 mg	140 g
Magnesium stearate	0.3 mg	2.1 g
Weight of granulation		919.1 g

Mix all the ingredients thoroughly. Compress into slugs. Grind and screen to 14–16-mesh granules. Recompress into tablets, using a $\frac{3}{16}$ -in. concave punch. 10 tablets should weigh 1.3 g.

CT Vitamin B-Complex

Ingredients	In each	In 10,000
Thiamine mononitrate ^a	0.733 mg	7.33 g
Riboflavin ^a	0.733 mg	7.33 g
Pyridoxine hydrochloride	0.333 mg	3.33 g
Calcium pantothenate ^a	0.4 mg	4 g
Nicotinamide	5 mg	50 g
Milk sugar (powder)	75.2 mg	752 g
Starch	21.9 mg	219 g
Talc	20 mg	200 g
Stearic acid (powder)	0.701 mg	7.01 g
Weight of granulation		1250 g

^a Includes 10% in excess of claim.

Mix all the ingredients thoroughly. Compress into slugs. Grind and screen to 14–16-mesh granules. Recompress into tablets, using a $\frac{3}{16}$ -inch concave punch. 10 tablets should weigh 1.25 g.

Sufficient tartaric acid should be used in these tablets to adjust the pH to 4.5.

Direct Compression Method**CT Ascorbic Acid USP, 250 mg**

Ingredients	In each	In 10,000
Ascorbic Acid USP (Mérck, fine crystals)	255 mg	2550 g
Microcrystalline cellulose ^a	159 mg	1590 g
Stearic acid	9 mg	90 g
Colloidal silica ^b	2 mg	20 g
Weight of granulation		4250 g

^a Avicel-PH-101.

^b Cab-O-Sil.

Blend all ingredients in a suitable blender. Compress using $\frac{3}{16}$ -in. standard concave punch. 10 tablets should weigh 4.25 g (courtesy, FMC).

Breath Freshener Tablets

Ingredients	In each	In 10,000
Wintergreen oil	0.6 mg	6 g
Menthol	0.85 mg	8.5 g
Peppermint oil	0.3 mg	3 g
Silica gel (Syloid 244 ^a)	1 mg	10 g
Sodium saccharin	0.3 mg	3 g
Sodium bicarbonate	14 mg	140 g
Mannitol USP (granular)	180.95 mg	1809.5 g
Calcium stearate	2 mg	20 g

^a Davison Chem.

Mix the flavor oils and menthol until liquid. Adsorb onto the silica gel. Add the remaining ingredients. Blend and compress on $\frac{3}{16}$ -in. flat-face bevel-edge punch to a thickness of 3.1 mm (courtesy, Atlas).

Chewable Antacid Tablets

Ingredients	In each	In 10,000
Aluminum hydroxide and Magnesium carbonate, co-dried gel ^a	325 mg	3250 g
Mannitol USP (granular)	675 mg	6750 g
Microcrystalline cellulose ^b	75 mg	750 g
Corn starch	30 mg	300 g
Calcium stearate	22 mg	220 g
Flavor	qs	qs

^a Reheis F-MA-11.

^b Avicel.

Blend all ingredients in a suitable blender. Compress using $\frac{3}{16}$ -in. flat-face bevel-edge punch (courtesy, Atlas).

Chewable Multivitamin Tablets

Ingredients	In each	In 10,000
Vitamin A USP (dry, stabilized form)	5000 USP units	50 million units
Vitamin D (dry, stabilized form)	400 USP units	4 million units
Ascorbic Acid USP	60.0 mg	600 g
Thiamine Hydrochloride USP	1 mg	10 g
Riboflavin USP	1.5 mg	15 g
Pyridoxine Hydrochloride USP	1 mg	10 g
Cyanocobalamin USP	2 μ g	20 mg
Calcium Pantothenate USP	3 mg	30 g
Niacinamide USP	10 mg	100 g
Mannitol USP (granular)	236.2 mg	2362 g
Corn starch	16.6 mg	166 g
Sodium Saccharin NF	1.1 mg	11 g
Magnesium stearate	6.6 mg	66 g
Talc USP	10 mg	100 g
Flavor	qs	qs

Blend all ingredients in a suitable blender. Compress using $\frac{3}{16}$ -in. flat-face bevel-edge punch (courtesy, Atlas).

CT Ferrous Sulfate

Ingredients	In each	In 7000
Ferrous Sulfate USP (crystal-line)	0.325 g	2275 g
Talc		0.975 g
Sterotex		1.95 g
Weight of granulation		2277.93 g

Grind to 12–14-mesh, lubricate, and compress. Coat immediately to avoid oxidation to the ferric state with 0.410 gr of tolu balsam (dissolved in alcohol) and 0.060 gr of salol and chalk. Use a deep concave $\frac{1}{32}$ -in. punch. 10 tablets should weigh 3.25 g.

CT Methenamine

Ingredients	In each, g	In 7000, g
Methenamine (12- to 14-mesh crystals)	0.325	2275
Weight of granulation		2275

Compress directly, using a $\frac{3}{16}$ -in. punch. 10 tablets should weigh 3.25 g.

CT Phenobarbital USP, 30 mg

Ingredients	In each	In 10,000
Phenobarbital	30.59 mg	305.9 g
Microcrystalline cellulose ^a	30.59 mg	305.9 g
Spray-dried lactose	69.16 mg	691.6 g
Colloidal silica ^b	1.33 mg	13.3 g
Stearic acid	1.33 mg	13.3 g
Weight of granulation		1330 g

^a Avicel-PH-101.

^b QUSO F-22.

Screen the phenobarbital to break up lumps and blend with microcrystalline cellulose. Add spray-dried lactose and blend. Finally add the stearic acid and colloidal silica; blend to obtain homogeneous mixture. Compress using $\frac{3}{16}$ -in. shallow concave punch. 10 tablets should weigh 1.33 g (courtesy, FMC).